REMARKS

With entry of this amendment, claim 20 has been amended and claim 22 has been cancelled. Support for the amendments to claim 20 can be found on page 15, lines 15-19 of the application as filed. No new matter has been added by way of these amendments.

Thus, after entry of these amendments, claims 2, 12, 13, and 17-21 remain pending and at issue.

Summary of Interview on July 1, 2011

Applicant thanks Examiner Draper for her time with the undersigned on Friday, July 1, 2011 to discuss the pending Office Action and, in particular, the obviousness rejections. The Declaration pursuant to 37 C.F.R. §1.132 by Dr. Richard Franklin ("the Franklin Declaration") filed September 19, 2007 and the Hansen reference (U.S. Patent No. 6,585,995) were discussed in view of the obviousness rejection.

Claim Rejection – 35 U.S.C. §112, second paragraph

Claim 20 has been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. *See* pages 3 of the Office Action. According to the Examiner, it is unclear if the "two distinct layers" recited in part (b) of the claim are (1) anagrelide or an anagrelide salt and (2) at least one adhesive or if the "two distinct layers" are (1) anagrelide or an anagrelide salt with at least one adhesive and (2) a single backing film.

Applicant has amended claim 20 to clarify that each layer of the multi-layer system contains both anagrelide or anagrelide salt and at least one adhesive and that the "two distinct layers" refers to multiple layers containing both anagrelide or anagrelide salt and at least one adhesive.

Claim 22 has been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. *See* pages 3-4 of the Office Action. Claim 22 has been cancelled rendering this rejection moot.

For at least these reasons, Applicant respectfully requests withdrawal of the indefiniteness rejections.

Claim Rejection - 35 U.S.C. §103

Claims 2, 12-13, and 17-20 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Anagrelide Study Group (*AM J Med,* 1992; 92:69-76; hereinafter "Anagrelide SG") in view of Hanson (U.S. Patent No. 6,585,995; hereinafter "Hanson"), Mitchel *et al.* ("Transdermal Drug Delivery-Clinical and Regulatory Strategies", *American Academy of Dermatology Annual Meeting*, March 2000; Abstract; hereinafter "Mitchel"), and Barnhart *et al.* (U.S. Patent No. 5,762,952; hereinafter "Barnhart"). *See* pages 5-10 of the Office Action. Claims 2, 12-13, 17, and 21 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Anagrelide SG in view of Hanson, Mitchel, and Zupon *et al.* (EP Patent No. 0252459; hereinafter "Zupon"). *See* pages 10-15 of the Office Action.

The Examiner asserts that one of ordinary skill in the art would treat thrombocythemia using anagrelide as taught by Anagrelide SG by administering anagrelide transdermally within a specific dosage range as disclosed by Hanson because Hanson teaches that transdermal administration reduces clinical toxicity. *See, e.g.*, pages 6-7 of the Office Action. Mitchel is cited by the Examiner to demonstrate that transdermal drug delivery avoids first pass liver metabolism and the resulting metabolites. *See, e.g.*, page 7 of the Office Action. Barnhart and Zupon are referenced by the Examiner as disclosing specific transdermal patches. *See* pages 9-10 and 15.

Applicant respectfully traverses these obviousness rejections. The amended claims would not have been obvious because, prior to the present invention, it was unknown that the severity of cardiovascular side effects observed when thrombocythemia patients are orally administered anagrelide was due to a metabolite (and in particular its 3-hydroxy metabolite). These

side effects are not trivial. A large number of patients orally treated with anagrelide fail to tolerate the drug. *See* ¶7 of Dr. Richard Franklin's Declaration submitted on September 19, 2007. The side effects of a drug can be due to a number of causes including the drug itself interacting with (unintended) receptors in the body. Without knowing the cause, a skilled artisan would not have known whether the cardiovascular side effects observed in thrombocythemia patients could be reduced, or how to do so. *See Eibel Process Co. v. Minnesota & Ontario Paper Co.*, 261 U.S. 45, 67-68 (1923) (Eibel discovered that defects in a newsprint paper making machine could be removed by changing the speed of the stock used to make the paper by using gravity. The Supreme Court found that Eibel discovered the problem that caused defective paper, and he then used known principles to fix that problem, stating that "[t]he invention was not the mere use of a high speed or substantial pitch to remedy a known source of trouble. It was the discovery of the source not before known, and the application of the remedy, for which Eibel was entitled to be rewarded in his patent.").

Surprisingly, however, Applicant discovered that transdermally administering anagrelide to treat thrombocythemia as recited in the claims minimizes the adverse cardiovascular side-effects observed when anagrelide is administered orally. These unpredictable results are discussed in the Franklin Declaration. Dr. Franklin's Declaration explains that Applicant determined the surprising cause of the adverse cardiovascular side-effects: the metabolite 3-hydroxy anagrelide. *See* ¶7 of the Franklin Declaration. The transdermal administration of anagrelide for treating thrombocythemia as recited in the pending claims reduces adverse cardiovascular side-effects compared to patients orally administered anagrelide by minimizing the amount of 3-hydroxy anagrelide formed during first-pass liver metabolism thereby reducing the plasma concentration of 3-hydroxy anagrelide compared to the plasma concentration of 3-hydroxy anagrelide after the oral administration of anagrelide. The reduction in the plasma concentration of 3-hydroxy anagrelide reduces the inhibition of phosphodiesterase III (PDEIII, an enzyme known to affect the cardiovascular system) by 3-hydroxy anagrelide resulting in the reduction in the adverse cardiovascular side-effects.

Dr. Franklin's Declaration provides 2 reasons for the non-obviousness of Applicant's invention. *See* ¶8 of the Franklin Declaration. First, 3-hydroxy anagrelide inhibited PDEIII to a greater than expected degree in view of the relatively minor change to the structure of anagrelide (*i.e.*, 3-hydroxy anagrelide inhibited PDEIII 40 times more potently than anagrelide). Second, the fact that the 3-hydroxy anagrelide metabolite causes undesirable side-effects represents the opposite of the expected metabolic detoxification process occurring in the liver.

Notably, as discussed above, cardiovascular side-effects are avoided when anagrelide is administered transdermally because this mode of administration minimizes the first pass liver metabolism of anagrelide into 3-hydroxy anagrelide. Thus, the invention does not depend on the type of the transdermal formulation used to administer the anagrelide.

None of the cited references, taken together or separately, disclose or suggest whether the cardiovascular side effects in thrombocythemia patients can be reduced or how these side effects in thrombocythemia patients can be reduced.

The Anagrelide SG reference discusses a study demonstrating that anagrelide could be used to control thrombocythemia. Patients were orally administered anagrelide. *See* page 70, column 1. While Anagrelide SG discloses the cardiovascular side effects of orally administered anagrelide on, *e.g.*, pages 73-74, Anagrelide SG does not disclose or suggest whether the observed cardiovascular side effects in thrombocythemia patients can be reduced or how to do so.

Similarly, Hansen should be disregarded as relevant art for at least 2 reasons. First, the Examiner cites to Hansen at column 18, lines 10-18 as teaching that anagrelide can be administered, *inter alia*, transdermally "without causing clinically unacceptable adverse events." *See, e.g.*, page 6 of the Office Action. Column 18, lines 10-18 are reproduced below:

> tion routes are available. The methods of the invention, generally speaking, may be practiced using any mode of administration that is medically acceptable, meaning any enteral or parenteral mode that produces effective levels of the active compounds without causing clinically unacceptable adverse effects. Such modes of administration include **oral**, rectal, topical, nasal, intrapulmonary, intracavitary,

transdermal, interdermal, transmucosal, subcutaneous, intravenous, intraarterial, intramuscular, or local routes. The

Emphasis added. The listing of both oral and transdermal modes of administration demonstrates that Hansen did not appreciate the difference between the oral and transdermal administration of anagrelide. Hansen did not understand that the mode of administration can influence the severity of cardiovascular side effects. In contrast, Applicant surprisingly recognized that the transdermal administration of anagrelide can reduce the cardiovascular side effects observed in patients with thrombocythemia who are orally administered anagrelide.

Second, as pointed out by the Examiner on, e.g., page 6 of the Office Action, Hansen discloses the treatment and prevention of vaso-occulsive events by reducing the platelet count of a patient to below normal levels. However, Hansen repeatedly notes that thrombocythemia patients are not intended to be within the scope of his invention. For example, column 9, line 67 to col. 10, line 5 states "[s]ubjects for whom the method of the invention are not intended are those diagnosed with conditions which already call for treatment with an agent such as anagrelide, i.e., secondary thrombocytosis, essential thrombocytosis, polycythemia vera, chromic myelogenous leukemia, and myelofibrosis." *See* also, *e.g.*, col. 2, lines 36-41, col. 6, lines 8-9, col. 9, lines 4-9, and col. 9, lines 46-55. Note that thrombocytosis and thrombocythemia are synonyms. *See* the definition of thrombocytosis submitted as Exhibit 2 in the response dated August 1, 2008. Hansen expressly excludes the treatment method recited in the claims: the treatment of thrombocythemia.

Mitchel, as explained by the Examiner on page 7 of the Office Action, discloses that the transdermal delivery of a drug avoids first pass liver metabolism compared to oral delivery. Mitchel does not disclose or suggest anagrelide, its use for the treatment of thrombocythemia, its side effects, or the reduction of its side effects.

Barnhart and Zupon both disclose transdermal drug delivery systems. Like Mitchel, Barnhart and Zupon do not disclose or suggest anagrelide, its use for the treatment of thrombocythemia, its side effects, or the reduction of its side effects.

As none of the cited references disclose or suggest that the severity of the cardiovascular side effects of anagrelide are due to its 3-hydroxy metabolite or that these side effects can be reduced in thrombocythemia patients, a skilled artisan would not have known or expected transdermal administration of anagrelide to significantly reduce these cardiovascular side effects in thrombocythemia patients. Accordingly, Applicant respectfully submits that the presently claimed method is non-obvious and respectfully requests withdrawal of this rejection.

Conclusion

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered, that the response be entered, and that all pending claims be allowed and the case passed to issue. If there are any other issues remaining which the Examiner believes could be resolved through a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below. If the undersigned is on leave, the Examiner is respectfully requested to contact Russell Garman (Registration No. 62,419) also of Frommer Lawrence & Haug at 212-863-2627.

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Respectfully submitted,

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